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Pulmonary Hypertension and Venous Thrombo-embolic Disease

INHIBITION OF FGFR SIGNALING WITH PD173074 AMELIORATES MONOCROTALINE-INDUCED PULMONARY ARTERIAL HYPERTENSION AND RESCUES BMPR-2 EXPRESSION

Poster Contributions
Poster Hall B1
Saturday, March 14, 2015, 10:00 a.m.-10:45 a.m.

Session Title: Epidemiology and Pathogenic Pathways in Pulmonary Arterial Hypertension
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Background: Fibroblast growth factor-2 (FGF-2) signaling plays a pivotal role in the development of pulmonary arterial hypertension (PAH).PD173074 is a potent FGF receptor 1 (FGFR-1) inhibitor that displays high activity and selectivity. The aim of this study was to investigate the effects of PD173074 on monocrotaline-induced PAH. We also evaluated whether FGFR-1 inhibition could attenuate bone morphogenetic protein type II receptor (BMPR-II) down-regulation.

Methods: PAH model was established by a single intraperitoneal injection of monocrotaline. And then a daily intraperitoneal injection of PD173074 (20 mg/kg) was administered from day 14 to day 28. Hemodynamic parameters, right ventricular hypertrophy index and morphometry were evaluated at day 28.

Results: The expression of FGF-2 and FGFR-1 was upregulated in lung tissue after monocrotaline injection, and it was accompanied by hemodynamic changes and pulmonary vascular remodeling. PD173074 treatment significantly ameliorated PAH and vascular remodeling (Figure A). It decreased ERK1/2 activation and rescued total Akt expression, leading to a reduction in both proliferation and apoptosis in the lung. Besides, PD173074 rescued the expression of BMPR-II (Figure B).

Conclusion: These results suggest that PD173074 can efficiently alleviate pulmonary arterial hypertension and it may be an useful option for PAH. Our data also suggest a role of FGF-2/BMP signaling interaction in PAH.